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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/487,023	01/19/2000	Parkash S. Gill	21327-701 CIP	2622

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McCutchen Doyle Brown & Enersen LLP
Three Embarcadero Center
San Francisco, CA 94111

EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/487,023	GILL ET AL.	
	Examiner	Art Unit	
	Sean R McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *24 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,9-12,16 and 20-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,9-12,16 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: oligonucleotide comparison diagram.

DETAILED ACTION

Claims 2, 9-12, 16, 20, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uchida et al [6,150,092] and Robinson et al [5,814,620; 5,710,136; and, 5,801,156].

The claimed invention is antisense oligonucleotides and compositions comprising antisense oligonucleotides for the inhibition of VEGF where there are several specific antisense sequences recited in the claims.

Uchida et al have taught methods of inhibiting VEGF with antisense oligonucleotides. The antisense oligonucleotides claimed by Uchida et al are targeted, for example, to the specific region of VEGF nucleic acid SEQ ID NO: 7. This region is 42 nucleotides long and is taught to be a preferred region on VEGF to target. All of the specifically recited antisense oligonucleotides of instant claims 2, 10, 12,16, and 24, for example, are all targeted to SEQ ID NO: 7 as taught by Uchida et al. The region taught by Uchida et al., is relatively small at 42 nucleotides in length. All of the recited antisense oligonucleotides of instant claims 2, 10, 12, 16 and 24 overlap, embrace, or are embraced by the specifically claimed antisense of Uchida et al claim 7, for example (SEQ ID NOS: 51, 54, 53, 50, 49, 138, and 141 of Uchida et al, for example). Attached is a diagram which shows the context of the prior art teachings of antisense to VEGF and the antisense oligonucleotides of the instant invention. Uchida et al have taught that the region defined by SEQ ID NO:7, to which all of the claimed oligonucleotides are

targeted, is a desirable region to target and is even referred to as a "core region" for targeting VEGF with antisense. Uchida et al further disclose pharmaceutical preparations for treatment of disease throughout their specification and claims. At columns 4 and 8-9 of Uchida et al, for example, pharmaceutical compositions, including various liposomal compositions, and methods of treatment with VEGF antisense oligonucleotides with phosphorothioate linkages are disclosed.

Robinson et al, in all of the three cited references, has demonstrated that antisense oligonucleotides targeted to VEGF have been known for use in various methods of treatment prior to applicants invention. It has been taught by Robinson et al that synthetic oligonucleotides of their invention [VEGF antisense] may be used in pharmaceutical preparation when combined with appropriate carrier, including liposomes (see 5,814,620, columns 9 and 11, for example) and phosphorothioate modifications (see columns 3, 7, 8, 12 and claims 3 and 4, of 5,814,620, for example).

Applicants claim limitations of a particular IC_{50} is not seen as providing a difference between the prior art antisense and that instantly claimed since no particular conditions for the cell cultures in the determination of such a value are required by the claims. This allows one in the art to set the conditions such that a particular IC50 value may be observed.

One in the art would clearly have had motivation to make the instantly claimed antisense molecules since it is absolutely clear that the region targeted has been clearly shown by the prior art to be a desired target for antisense inhibition of VEGF. One in the art would clearly look to the SEQ ID NO: 7 region in the making of antisense

targeted to VEGF and the optimization of antisense to VEGF, for example. The specific antisense claimed are not only targeted to the specifically taught target sequence but many overlap, embrace or are embraced by the specific VEGF antisense taught by Uchida et. One in the art would clearly look to these specific regions to make antisense oligonucleotides to inhibit VEGF since the specific region has clearly been shown to be an effective target region and antisense to this target have been clearly taught in the art to be effective antisense oligonucleotides. One in the art would clearly look to the region taught by Uchida to be a "core region" for antisense targeted to VEGF to optimize antisense targeted to VEGF, for example.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Claims 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uchida et al., Robinson et al [US 5,814,620], Barleon et al [Blood Vol. 87, No. 8:3336-3343, 4/15/96] and Chan et al [The American journal of Surgical Pathology Vol. 22(7):816-826, 1998].

Uchida et al is relied upon as above and further for the following: It has been taught at column 1, for example, that ". . .inhibition of the vascular endothelial growth factor leads to inhibition of growth of solid tumor cells, and this should be applicable in the development of anticancer agents. [I]n fact there is a report on a method to use an anti-VEGF antibody"

Robinson et al has demonstrated that antisense oligonucleotides targeted to VEGF have been known for use in various methods of treatment prior to applicants invention and that it was known to use liposome formulations for pharmaceutical preparations of antisense oligonucleotides (see column 9, for example). It has been taught by Robinson et al that synthetic oligonucleotides of their invention [VEGF antisense] may be used in pharmaceutical preparation when combined with appropriate carrier. It is further taught that such compositions can include other factors and/or agents which enhance inhibition of VEGF expression or which will reduce neovascularation (see columns 8 and 9, for example). It has been taught by Robinson et al that synthetic oligonucleotides of their invention [VEGF antisense] may be used in pharmaceutical preparation when combined with appropriate carrier. It is further taught that such compositions can include other factors and/or agents which enhance inhibition of VEGF expression or which will reduce neovascularation (see columns 8 and 9, for example).

Barleon et al taught inhibition of VEGF via specific antiserum and the role of flt-1 with VEGF biopathway.

Chan et al have taught the Association of VEGF and its receptors and their roles in various diseases.

Applicants claim limitations of a particular IC_{50} is not seen as providing a difference between the prior art antisense and that instantly claimed since no particular conditions for the cell cultures in the determination of such a value are required by the

claims. This allows one in the art to set the conditions such that a particular IC50 value may be observed.

It would have been obvious to use antibodies in conjunction with antisense targeted to VEGF since the prior art has taught antisense to inhibit VEGF, antibodies to inhibit VEGF and since the art has taught that VEGF receptors are associated with the same disease sates as VEGF. The art has taught that one in the art can combine other VEGF inhibitors in combination with VEGF antisense. Since the art has shown inhibition of VEGF by antisense and via antibodies one in the art would have a reasonable expectation of the successful use of a combination of such a combination and further to simply combine different antisense targeted to the same target, for example. Furthermore it is prima facie obvious to combine two composition each of which has been taught in the art to be useful for the same purpose (see MPEP2144.06, for example).

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Applicant's arguments filed 5/24/04 have been fully considered but they are not persuasive.

The Declaration of Dr. Gill has not been considered since no executed copy has been submitted prior to this Official Action. Applicant arguments are addressed minus their reliance on the declaration.

Applicant argues that Uchida et al do not teach the exact sequence of SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28, and 29 and do not teach these sequences with phosphorothioate modifications. It is noted that the sequences are not specifically disclosed by Uchida et al or the rejection would be under 35 U.S.C. 102 as opposed to the rejection under 35 U.S.C. 103. Even though the specific sequences have not been specifically disclosed they are indeed variations on what has been taught in the art. Again it is noted that applicant has not provided any evidence that the specific antisense claimed have any activity that would be unexpected over what has been taught in the prior art. A review of the Attachment provided a clear picture of how small the target region is and how applicant specific sequences are all meshed within the specific target region taught by Uchida and the specific antisense oligonucleotides of Uchida. It is noted that the diagram in the Attachment is not an exhaustive comparison, but still provides a clear picture of the instantly claimed oligonucleotides in comparison to that taught in the art. Uchida et al and Robinson have both taught phosphorothioate modifications and have taught how they are beneficial for use in therapeutic applications. The art has clearly shown a motivation to modify antisense oligonucleotides for use in therapies, for example. It is clear that Uchida et al intended for their antisense oligonucleotides to be used in vivo. Applicant argues that the antisense modified by Uchida et al do not work well in cells. This is merely an opinion with no data (i.e. comparative: this point of comparative analysis between the prior art and the instant compounds has been made by the examiner in all answers to applicant arguments) that would show that this would be fact. Applicant's argument as to the

"poor effectiveness" of the antisense of Uchida as compared to the antisense instantly claimed antisense has not been demonstrated. Applicant does not compare that which can be properly compared. A side-by-side analysis of those antisenses in the art and those specifically claimed would provide a better position for the determination of any unexpected results. As the record stands there are not unexpected properties shown for the instantly claimed oligonucleotides compared to those taught in the prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

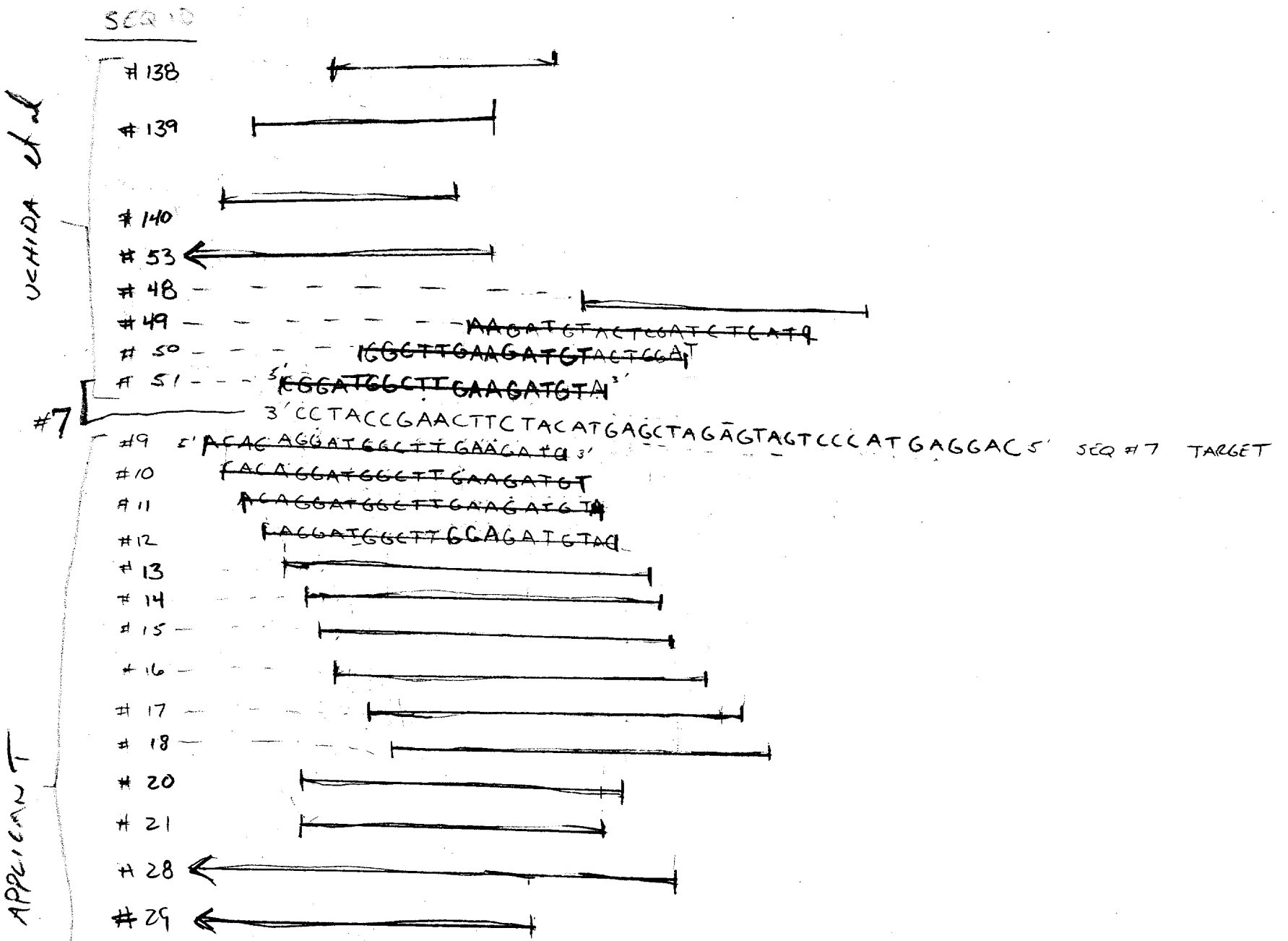
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sean R McGarry
Primary Examiner
Art Unit 1635

SRM

PLEASE SCAN THIS IS A PART OF THE OFFICIAL RECORD FOR APPLICATION 09/487,023.



UCHIDA et al

APPLICANT

ATTACHMENT TO FINAL REJECTION 20040803